STATISTICS FILING MEMORANDUM FOR A SUPPLEMENTAL NDA

sNDA:	21-225
Drug Name:	Mirena™ (Intrauterine system, 52 mg)
Sponsor:	Bayer HealthCare Pharmaceuticals Inc.
Indications:	Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception
Medical Officer:	Gerald D Willett, M.D., Division of Reproductive and Urologic Product
Statistician:	Xin Fang, Ph.D., HFD-725, Division of Biometrics 3
Project Manager:	Charlene Williamson
Submission Date:	03/31/2009
45 day Meeting Date:	05/11/2009

A: Summary of Clinical Studies

The objective of this filing review is to determine whether this NDA is sufficiently complete for substantive statistical review. As part of the determination, we verify the format and contents of the efficacy and safety data sets that will allow us to perform pertinent statistical analysis as per study protocol. The sponsor submitted nine active-control-without-placebo studies to support the efficacy of Mirena™ in the treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception. These studies are all open-label and are listed below.

1. Study A36340, entitled "A randomized, open-label, multicentre, study comparing the efficacy and safety of Mirena® to Minestrin™ over a 12-month period in women aged over 30 with functional menorrhagia." (Protocol 302760)
2. Study BC71, entitled "Randomized comparative controlled study comparing the efficacy of Levonova® with surgical treatment of menorrhagia by transcervical endometrial resection. Final report of 36-month data." (Protocol LE102-93503 (-02))
3. Study A00696, entitled "Randomized, open-label, multicenter study comparing the efficacy and safety of Mirena to a three-month administration of danazol followed by a 3-month observation period in women aged over 30 with functional menorrhagia" (Protocol DE00650-303003)
4. Study A14096, entitled "Randomized Comparative Study of the Efficacy of the Levonorgestrel IUS and Oral Mefenamic Acid for the Treatment of Idiopathic Menorrhagia. Full Report Including both the Comparative Part of the Study and the Extended Follow-Up for the LNG IUS Group." (Protocol LE102-93547 (-02))
5. Study A00630, entitled "Randomized comparative study of the efficacy of levonorgestrel IUS and oral tranexamic acid for the treatment of idiopathic menorrhagia. Final report on 12-cycle data." (Protocol LE102-94548 (-02))
6. Study A02916, entitled "Efficacy and safety of the levonorgestrel intrauterine system ompared with oral norethisterone in the treatment of idiopathic mernorrhagia. Final abbreviated report on LNG IUS subjects." (Protocol LE102-92549 (-02))
7. Study B088, entitled "Efficacy and safety of the levonorgestrel intrauterine system compared with oral norethisterone in the treatment of idiopathic menorrhagia"
8. **Study A38313**, entitled "A multicenter, randomized, open label, parallel group, active

control study to evaluate the efficacy and safety of LNG IUS (Mirena) as compared to edroxyprogesterone acetate during 6 cycles of treatment in patients with idiopathic menorrhagia" (Protocol 309849)

9. Study B086, entitled "Conservative treatment of excessive uterine bleeding and dysmenorrheal with levonorgestrelius as an alternative to hysterectomy"

The sponsor planned to use Study A38313 (Protocol 309849) as the pivotal study for efficacy evaluation. Although this study was not blinded and not placebo-controlled, FDA agreed with the sponsor's protocol due to ethical and other reasons (meeting minutes dated on Jan 12, 2009).

B: Conclusion

After the preliminary review of the submission for the following items in the checklist, we have determined that this NDA is fileable.

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			NA for Gender
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).		√		No tabulation datasets

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.		√		Not blinded
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

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/s/

XIN FANG
09/29/2009

SONIA CASTILLO
09/29/2009
Signing for Mahboob Sobhan